

# Antiretroviral therapy and liver disorders in the OPERA<sup>®</sup> cohort

Michael Wohlfeiler, Karam Mounzer, Laurence Brunet<sup>ID</sup>, Jennifer Fusco<sup>ID</sup>, Vani Vannappagari, Lloyd Curtis, Nassrin Payvandi, Michael Aboud, Ricky Hsu, Philip Lackey and Gregory Fusco

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## Abstract

**Introduction:** A comprehensive assessment of liver disorders was conducted among people living with HIV (PLWH) on a new antiretroviral regimen based on common core agents.

**Methods:** Treatment-naïve and experienced PLWH first initiating dolutegravir (DTG), elvitegravir (EVG), raltegravir (RAL), or darunavir (DRV) in the OPERA<sup>®</sup> cohort were included if they had  $\geq 1$  liver chemistry test performed both within 12 months before regimen start and over follow-up. Liver disorders were defined as a diagnosis of drug-induced liver injury (DILI) or moderate/severe liver chemistry elevations (LCE). History of liver disorders experienced within 12 months of initiation was summarized. Liver disorders occurring during follow-up were described as prevalent (all disorders) or incident (disorders occurring among PLWH without a history of liver disorders or advanced liver fibrosis).

**Results:** Out of 16,024 PLWH, 38% initiated DTG, 43% EVG, 5% RAL, and 14% DRV. EVG users were younger and had a lower likelihood of comorbidities or lipid-lowering agent use than DTG users. EVG users were significantly less likely to have a history of moderate/severe LCE or to have prevalent moderate LCE. RAL users were older and had a higher likelihood of comorbidities or lipid-lowering agent use than DTG users. RAL users were significantly more likely to have a history of advanced liver fibrosis and prevalent moderate/severe LCE during follow-up. DRV users were older and had a lower likelihood of lipid-lowering agent use than DTG users. There was no difference in history of LCE, nor in prevalent or incident LCE between DRV and DTG users. No DILI diagnoses were recorded. Discontinuation following a liver disorder was rare ( $< 1\%$ ) across all groups.

**Conclusion:** While PLWH with comorbidities may have been channeled away from EVG and toward DTG and RAL, the incidence of moderate/severe LCE did not differ between DTG and EVG, RAL, and DRV.

**Keywords:** antiretroviral therapy, drug-induced liver injury, HIV, liver chemistry elevation, liver disorders

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Correspondence to:  
**Laurence Brunet**  
Epididian, Inc., 4819  
Emperor Blvd. Ste 400,  
Durham, NC 27703, USA  
[laurence.brunet@epididian.com](mailto:laurence.brunet@epididian.com)

**Michael Wohlfeiler**  
AIDS Healthcare  
Foundation, Miami, FL,  
USA

**Karam Mounzer**  
Philadelphia FIGHT,  
Philadelphia, PA, USA

**Jennifer Fusco**  
**Gregory Fusco**  
Epididian, Inc., Durham,  
NC, USA

**Vani Vannappagari**  
ViiV Healthcare, Research  
Triangle Park, NC, USA

**Lloyd Curtis**  
GlaxoSmithKline, London,  
UK

**Nassrin Payvandi**  
**Michael Aboud**  
ViiV Healthcare, Brentford,  
London, UK

**Ricky Hsu**  
NYU Langone Medical  
Center, New York, NY, USA

AIDS Healthcare  
Foundation, New York,  
NY, USA

**Philip Lackey**  
Signature Healthcare,  
Charlotte, NC, USA

## Plain language summary

### Liver disorders and HIV treatment

A comprehensive assessment of liver disorders was conducted using data from the OPERA<sup>®</sup> cohort, which provides anonymous patient-level clinical data from electronic health records. People living with HIV (PLWH) who were starting a new HIV treatment regimen that included one of four common HIV drugs were included in this study. Liver disorders included drug-induced liver injury (DILI) and moderate or severe liver chemistry elevations. History of a disorder was defined as liver disorders that occurred before starting the new treatment. Prevalent disorders

were those that occurred after starting the new treatment in the whole population. Incident disorders were those that occurred after starting the new treatment, but only among PLWH without any history of liver disorders.

Out of 16,024 PLWH, 38% initiated dolutegravir (DTG), 43% elvitegravir (EVG), 5% raltegravir (RAL), and 14% darunavir (DRV). EVG users were younger and less likely to have other diseases or use cholesterol lowering drugs compared to DTG users. They were also less likely to have a history of moderate/severe liver chemistry elevations or to have prevalent moderate liver chemistry elevations. RAL users were older and more likely to have other diseases or use cholesterol lowering drugs compared to DTG users. They were also more likely to have prevalent moderate/severe liver chemistry elevations than DTG users. DRV users were older and less likely to use cholesterol lowering agents compared to DTG users. There was no difference in history of liver chemistry elevations, or in prevalent, or incident liver chemistry elevations between DRV and DTG users. There were no DILI diagnoses and discontinuation of treatment following liver disorders was rare across all groups. Overall, the incidence of liver disorders after starting a new HIV treatment regimen did not differ between four common antiretroviral drugs.

### Introduction

With modern antiretroviral therapy (ART), life expectancy of people living with HIV (PLWH) has improved.<sup>1</sup> However, certain comorbid conditions [e.g. infection with chronic hepatitis C virus (HCV)] remain more likely among PLWH than in the general population.<sup>2,3</sup> Possible toxicity must be considered with multi-drug regimens and pharmacokinetic interactions with medications for comorbidities, and adverse drug reactions are still a common occurrence.<sup>4</sup> Though declining, liver disease is still a leading cause of death among PLWH.<sup>5</sup> Many trials assessing the safety and efficacy of modern ART have reported low frequencies of liver disorders following the initiation of common antiretroviral (ARV) drugs.

Randomized trials focusing on the treatment-naïve population have reported low liver chemistry elevations (LCE) frequencies, with various enzymes measured. Grade 3–4 LCE was 1% over 144 weeks after dolutegravir (DTG) initiation,<sup>6</sup> <1% over 48–144 weeks after elvitegravir (EVG) initiation,<sup>6,7</sup> and 1% over 192 weeks after ritonavir-boosted darunavir (DRV/r) initiation.<sup>8</sup> With raltegravir (RAL) initiation, incidence of grade 3–4 LCE was 5% over 48 weeks; incidence of LCE was up to 2% (grade 3) and up to 1% (grade 4) over 96 weeks.<sup>9,10</sup>

Similarly, LCE has been reported as a rare occurrence in clinical trials of treatment-experienced PLWH. With a switch to EVG, the incidence of grade 3–4 LCE was 2% over 48 weeks.<sup>11</sup> As for RAL, grade 3 LCE was reported in up to 4%, and

grade 4 LCE was reported in up to 1% of experienced PLWH over 96 weeks after switch.<sup>12</sup> Lastly, grade 2–4 LCE ranged from 7% to 9% over 48 weeks with DRV/r.<sup>13</sup> DRV/r has also been associated with drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis).<sup>14</sup>

However, there are limited studies evaluating the occurrence of liver outcomes following ART initiation among PLWH in an observational setting. In the SCOLTA cohort, the incidence of grade 3–4 LCE, defined by aspartate transaminase (AST) and alanine aminotransferase (ALT) levels, was reported as 1% for both 78 treatment-naïve patients and 202 treatment-experienced patients initiating EVG.<sup>15</sup> In the ICONA Cohort, moderate or severe LCE was associated with initiation of a non-nucleoside reverse transcriptase inhibitor (NNRTI), compared with an integrase strand transfer inhibitor (INSTI) in ART-naïve PLWH, although no difference between core agent groups was detected for severe LCE.<sup>16</sup> Finally, among RAL users in Spain, grade 3–4 hepatotoxicity was developed by 1%; all incident cases were attributed to HCV co-infection.<sup>17</sup> Though several studies have reported on the hepatic safety of common ART regimens in a trial setting, more research on liver outcomes among PLWH within an observational setting is warranted.

With increasing INSTI use across diverse populations and clinical situations, clinicians will benefit from a better understanding of the overall hepatic safety profile of common ARVs. Such additional insight may guide clinicians in designing the most

appropriate treatment strategies for PLWH. The objective of this study was to describe the occurrence of liver outcomes among PLWH starting an ART regimen that contained one of four common core agents (i.e. DTG, EVG, RAL, DRV) in a population-based cohort of PLWH in care in the United States (US).

## Methods

### *Study population and design*

The Observational Pharmacoepidemiology Research and Analysis (OPERA<sup>®</sup>) cohort is a database utilizing prospectively collected electronic health record (EHR) data. OPERA complies with all HIPAA and HITECH requirements and receives annual institutional review board approval by Advarra IRB (#CR00173408), including a waiver of informed consent and authorization for use of protected health information. At the time of this study, there were over 80,000 individuals in the OPERA cohort with HIV infection in routine clinical care at 79 out-patient clinics across 15 US states. The OPERA cohort reflects routine medical care. Decisions regarding visits, testing, and prescriptions decisions are made by the treating providers and patients and recorded in the EHR. These data are then retrieved, cleaned, aggregated, and anonymized to maintain patient confidentiality in the OPERA cohort.

All ART-naïve or experienced PLWH were at least 13 years of age, first initiating an ART regimen containing DTG, EVG, RAL, or DRV between 1 August 2013 and 31 December 2016, and were included if they had at least one liver chemistry test performed within the 12 months before starting the regimen and at least one performed during follow-up. PLWH were observed from baseline (date of core agent initiation) until the first of the following censoring events: discontinuation of core agent, 12 months after their last clinical contact, death, or study end (31 December 2017).

### *Outcomes*

Liver disorders were defined as a drug-induced liver injury (DILI) diagnosis or a moderate or severe LCE. Diagnoses of DILI were identified using text searches of the diagnosis field of the EHR. Moderate LCE was defined according to the DAIDS rating scale as grade 2 [ALT, AST, alkaline phosphatase (ALP)  $\geq 2.5$  to  $< 5 \times$  upper

limit of normal (ULN); bilirubin  $\geq 1.6$  to  $< 2.6 \times$  ULN].<sup>18</sup> Severe LCE was defined according to the DAIDS rating scale as grade 3 or 4 (ALT, AST, ALP  $\geq 5 \times$  ULN; bilirubin  $\geq 2.6 \times$  ULN).<sup>18</sup> Advanced liver fibrosis was defined as a score  $> 3.25$  on the Fibrosis-4 (Fib-4) Index.

A history of liver disorders consisted of an event occurring up to 12 months before or at baseline. A prevalent disorder was defined as an event occurring over the course of follow-up, whether PLWH had a history of any disorder for the given organ system or not. An incident disorder was defined as only a new event occurring after baseline, excluding PLWH who had any history of liver disorder; incident disorders were a subset of prevalent disorders. Regimen discontinuation was defined as a core agent discontinuation within 21 days after a liver disorder.

### *Statistical analyses*

Baseline characteristics, as well as baseline and follow-up occurrence of liver disorders, were described by core agent of interest. *p*-values were calculated with the Pearson's Chi-Square (categorical variables), the Mann-Whitney Test (continuous variables), or the Fisher Exact test (categorical variables with cells with counts of five or fewer). The Sidak Correction was applied to account for multiple comparisons between DTG and comparator core agents. The adjusted alpha level for significance was 0.017.

## Results

Among 16,024 PLWH in the overall study population, baseline demographic and clinical characteristics differed across core agent groups (Table 1). The majority of PLWH in the sample were on EVG (43%) or DTG (38%), followed by DRV (14%) and RAL (5%). PLWH in the RAL and DRV groups were older, more likely to be women and more likely to be ART-experienced compared with the DTG group. PLWH in the EVG group were younger and more likely to be ART-naïve compared with the DTG group. At baseline, the regimen of interest was less likely to contain an additional core agent for EVG (7%) and DRV users (9%), and more likely for RAL users (35%), compared with DTG users (13%). EVG users (11%) were less likely and RAL users (22%) more likely to have prevalent liver disease compared with DTG users (15%) (Table 1).

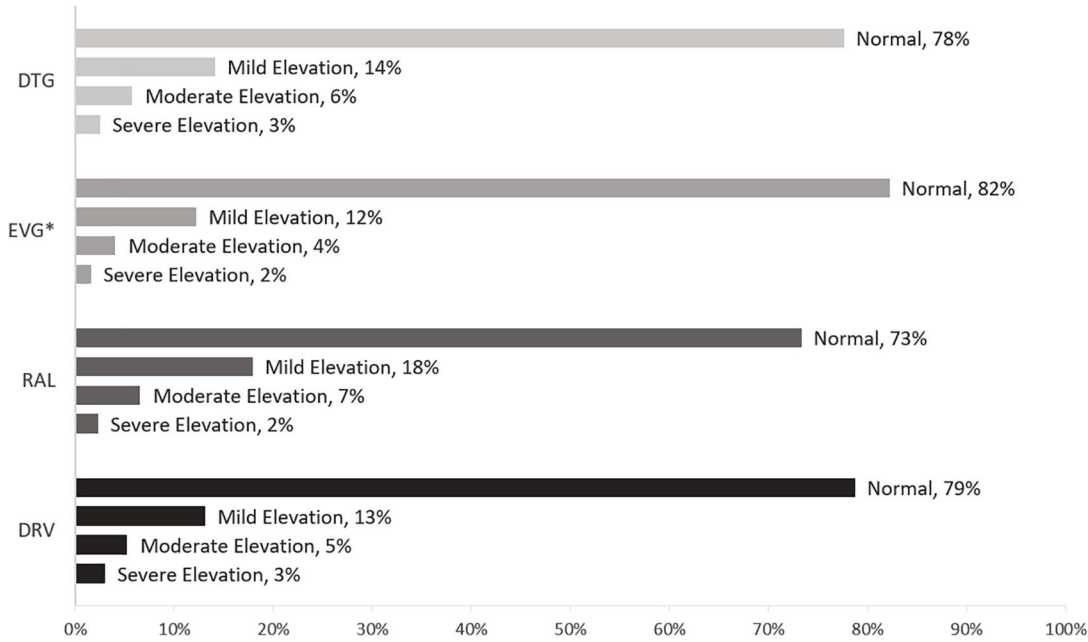
**Table 1.** Baseline demographic and clinical characteristics by core agent group ( $n = 16,024$ ).

	DTG ( $n = 6102$ )	EVG ( $n = 6899$ )	RAL ( $n = 827$ )	DRV ( $n = 2196$ )
Age, median (IQR)	41 (29, 51)	36 (27, 48)*	48 (39, 54)*	43 (33, 51)*
Male, $n$ (%)	5221 (86)	5965 (87)	659 (80)*	1730 (79)*
African American, $n$ (%)	2479 (41)	2866 (42)	299 (36)*	1056 (48)*
Payer, $n$ (%)				
Medicaid	1407 (23)	1159 (17)*	202 (24)	547 (25)
ADAP/Ryan White	2374 (39)	2564 (37)	244 (30)*	788 (36)*
ART- naive	2236 (37)	2858 (41)*	143 (17)*	715 (33)*
Viral load ( $\log_{10}$ ), median (IQR)	2.6 (1.3, 4.6)	3.3 (1.3, 4.7)*	1.3 (1.3, 3.0)*	3.0 (1.3, 4.7)*
CD4 count (cells/ $\mu$ L), median (IQR)	494 (311, 710)	489 (306, 698)	516 (310, 741)	387 (187, 631)*
Regimen containing >1 core agent, $n$ (%)	780 (13)	455 (77)*	292 (35)*	207 (9)*
VACS Index <sup>†</sup> , median (IQR)	17 (7, 29)	13 (7, 25)*	20 (10, 34)*	22 (12, 39)*
Comorbid conditions, $n$ (%) <sup>‡</sup>	4643 (76)	4739 (69)*	704 (85)*	1664 (76)
Liver disease, $n$ (%) <sup>§</sup>	928 (15)	744 (11)*	184 (22)*	369 (17)
Hepatitis B, $n$ (%)	306 (5)	329 (5)	46 (6)	163 (7)*
Hepatitis C, $n$ (%)	581 (10)	359 (5)*	126 (15)*	204 (9)
Use of lipid-lowering agents, $n$ (%)	935 (15)	694 (10)*	165 (20)*	247 (11)*
* $p$ -value < 0.017 for the comparison with dolutegravir.				
<sup>†</sup> VACS Index is a score calculated based on a person's age, CD4 count, HIV-1 RNA, hemoglobin, platelets, aspartate and alanine transaminase, creatinine, and viral hepatitis C infection. Higher VACS scores are associated with a higher risk of 5-year all-cause mortality.				
<sup>‡</sup> Cardiovascular disease (arrhythmia, myocardial infarction, angina, other/unspecified CHD, occlusion/stenosis of precerebral arteries, stroke, transient ischemic attack, other cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm), invasive cancer, endocrine disorders (diabetes mellitus, hyperlipidemia, hyperthyroidism, hypothyroidism, thyroiditis), mental health conditions (anxiety disorders, bipolar or manic disorders, major depressive disorder, schizophrenic disorder, dementia, suicidality), liver diseases (hepatitis B, hepatitis C, other chronic liver disease), bone disease, peripheral neuropathy, renal disease (renal impairment, moderate/severe chronic kidney disease, end stage renal disease), hypertension, rheumatoid arthritis, alcohol/drug dependence/abuse.				
<sup>§</sup> Hepatitis B, hepatitis C, or other chronic liver disease.				
ART, antiretroviral therapy; DRV, darunavir; DTG, dolutegravir; EVG, elvitegravir; IQR, interquartile range; RAL, raltegravir; VACS, Veterans Aging Cohort Study.				

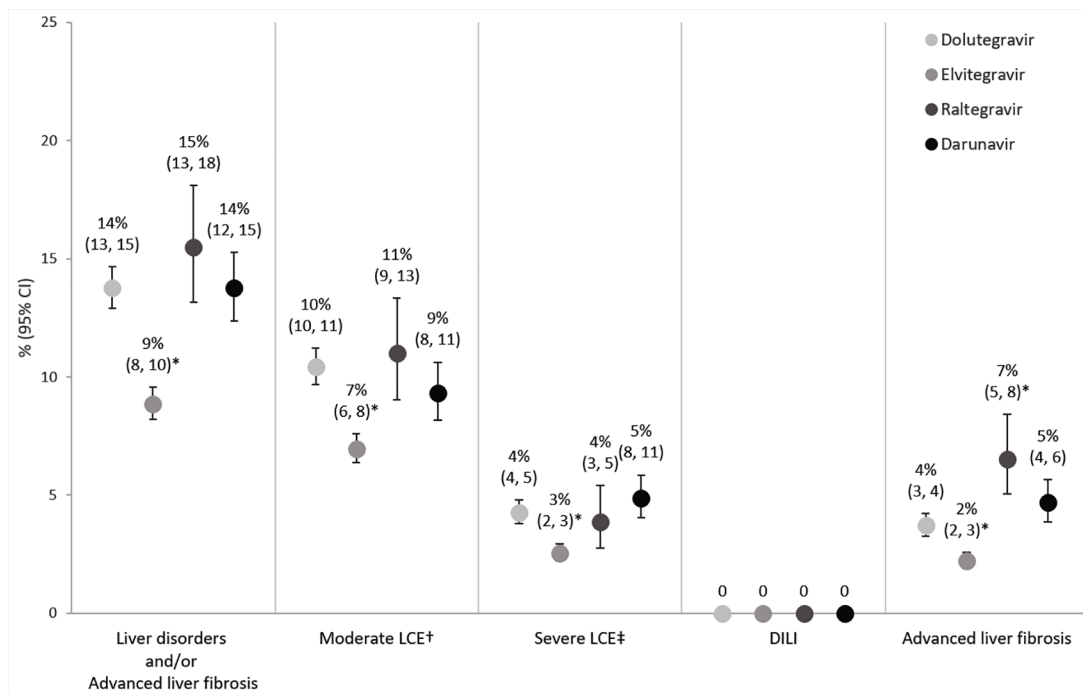
The majority of PLWH had baseline liver chemistry values within the normal range (Figure 1). The proportion of PLWH with a mild or moderate LCE at baseline was highest for RAL users (18% and 7%, respectively), followed by DTG users (14% and 6%, respectively). However, DRV and DTG users had the highest proportion of PLWH with a severe LCE at baseline (3%) compared with those on RAL and EVG (2%).

The categorical distribution of liver chemistry values reached statistical significance for the comparison between EVG and DTG only.

As shown in Figure 2, EVG users had the lowest proportion of a history of liver disorders or advanced liver fibrosis within the 12-month period prior to baseline (9%) compared with DTG users (14%;  $p < 0.017$ ). After evaluating each outcome



**Figure 1.** Distribution of baseline liver chemistry elevations<sup>†</sup> (*n* = 16,024) DRV, darunavir; DTG, dolutegravir; EVG, elvitegravir; RAL, raltegravir.  
<sup>†</sup>Normal: AST/ALT/ALP <1.25× ULN and bilirubin <1.1× ULN; Mild Elevation: AST, ALT or ALP ≥1.25 to <2.5× ULN or bilirubin ≥1.1 to <1.6× ULN; Moderate Elevation: AST, ALT or ALP ≥2.5 to <5× ULN or bilirubin ≥1.6 to <2.6× ULN; Severe Elevation: AST, ALT or ALP ≥5× ULN or bilirubin ≥2.6× ULN.  
<sup>\*</sup>*p*-value <0.017 for the comparison with dolutegravir.



**Figure 2.** Baseline history of liver disorders and liver fibrosis (*n* = 16,024).  
<sup>\*</sup>*p*-value <0.017 for the comparison with dolutegravir.  
<sup>†</sup>Moderate Elevation: AST, ALT or ALP ≥2.5 to <5× ULN or bilirubin ≥1.6 to <2.6× ULN.  
<sup>‡</sup>Severe Elevation: AST, ALT or ALP ≥5× ULN or bilirubin ≥2.6× ULN.  
<sup>§</sup>Advanced Liver Fibrosis: Fib-4 Index >3.25.  
 CI, confidence interval; DILI, drug-induced liver injury; LCE, liver chemistry elevation.

separately, EVG users had a lower likelihood of moderate or severe LCE history, or of advanced liver fibrosis history, compared with DTG users (all  $p < 0.017$ ). More specifically, EVG users had statistically significant lower likelihood of moderate or severe bilirubin elevations and severe ALT elevations than DTG users (Table 2). RAL users had a higher likelihood of advanced liver fibrosis history compared with DTG users (7% versus 4%;  $p < 0.017$ ). RAL users were also statistically more likely to have moderate ALT or AST elevations than DTG users (Table 2). There were no PLWH with a history of DILI, and no other significant differences between groups.

Prevalent liver outcomes by each core agent are displayed in Figure 3. Prevalent liver disorders, moderate LCE, and severe LCE were more likely among RAL users (14%, 13% and 5%, respectively), compared with DTG users (10%, 9% and 3%, respectively). Prevalent liver disorders (7%) and moderate LCE (7%) were less likely among EVG users than DTG users. No prevalent or incident cases of DILI were recorded (Figure 3). In terms of specific LCE (Table 3), moderate elevations of ALT or bilirubin, as well as severe elevations of bilirubin, were less likely with EVG than with DTG. Compared with DTG, PLWH on RAL had a higher likelihood of moderate ALT, AST or bilirubin elevations, as well as severe bilirubin elevations. DRV users were statistically less likely to have moderate ALP or bilirubin elevations compared with DTG users.

Incident liver outcomes are displayed in Figure 4. No difference in incident liver disorders was detected between DTG and any other group. However, when assessing specific LCE (Table 4), compared with DTG users, EVG users were less likely to have moderate bilirubin elevations; RAL users were more likely to have moderate bilirubin elevations; and DRV users were more likely to have moderate ALP elevations. There were very few core agent discontinuations within 21 days after a prevalent liver disorder (DTG: 0.6%, EVG: 0.4%, RAL: 0.7%, DRV: 0.9%) or an incident disorder (DTG: 0.3%, EVG: 0.2%, RAL: 0.2%, DRV: 0.7%); no statistically significant difference was detected between groups.

### Discussion

Out of 16,024 PLWH starting a core agent of interest between 1 August 2013 and 31 December 2016 (with follow-up extending through 31

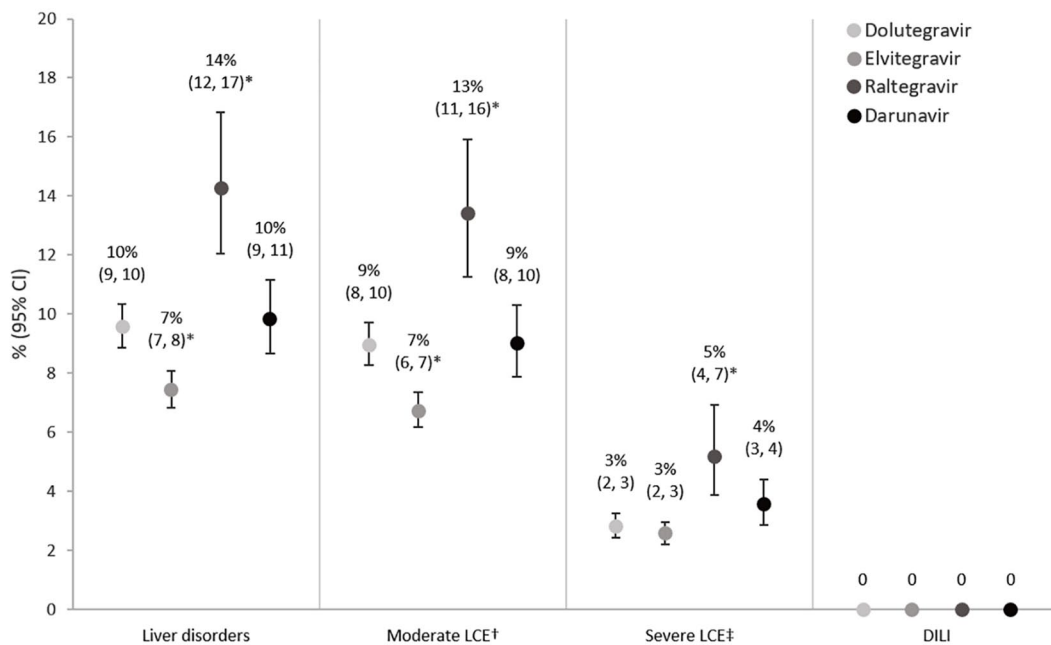
December 2017), 6102 (38%) started DTG, 6899 (43%) started EVG, 827 (5%) started RAL, and 2196 (14%) started DRV. Many demographic and clinical baseline characteristics differed across core agent groups. PLWH on EVG were younger, more likely to be ART-naïve, and less likely to have comorbidities or LCE at baseline compared with PLWH on DTG. Over follow-up, prevalent liver disorders and moderate LCE were less likely with EVG than with DTG. PLWH prescribed RAL were older and more likely to be ART-experienced, have comorbidities (including liver diseases), and use lipid-lowering agents than PLWH on DTG. RAL users also had a higher likelihood of prevalent liver disorders or moderate LCE during follow-up than DTG users. Though DRV users were older, less likely to take lipid-lowering agents, and were sicker than DTG users, they experienced a similar proportion of prevalent liver outcomes. Incident disorders did not differ by core agent, even though statistically significant differences in history and prevalence of liver disorders were detected. Finally, discontinuation rarely occurred following liver disorders (<1%) and did not differ by core agent group.

Results from the OPERA cohort are consistent with those reported by randomized trials, two of which were performed among ART-naïve PLWH and compared DTG or EVG with RAL. The SPRING-2 trial of 411 PLWH randomized to DTG or RAL reported a total of four severe LCE and two possible DILI over 48 weeks; there were no new events over the subsequent 48 weeks of follow-up and no differences between the groups.<sup>19,20</sup> In a phase III trial of PLWH randomized to EVG ( $n=351$ ) or RAL ( $n=351$ ), the incidence of severe LCE (ALT or AST) was higher in the RAL group (5%) than in the EVG group (1–2%); seven PLWH in the RAL group experienced a grade 4 elevation of AST compared with only one PLWH in the EVG group.<sup>9</sup> At 48 weeks in the SINGLE trial of ART-naïve PLWH, 2% of PLWH experienced a moderate or severe elevation of ALT; results were similar for AST. By 144 weeks, only six (1%) had experienced a severe elevation of ALT, but those were attributed to HCV or other hepatotoxic medications.<sup>6,21</sup> In the SWORD-1 and SWORD-2 trials among 513 ART-experienced, virologically suppressed PLWH taking DTG, the incidence of liver disorders was even more rare (<1%).<sup>22,23</sup> In trials of EVG users, incidence of moderate LCE among ART-naïve PLWH was <1%<sup>7,24</sup> and only 2% of ART-experienced PLWH in the STRATEGY-PI study experienced a

**Table 2.** Baseline history of specific liver chemistry elevations ( $n = 16,024$ ).

	DTG ( $n = 6102$ )	EVG ( $n = 6899$ )	RAL ( $n = 827$ )	DRV ( $n = 2196$ )
History of moderate liver chemistry elevation, $n$ (%) <sup>†</sup>				
ALT	208 (3)	215 (3)	45 (5)*	77 (4)
AST	187 (3)	172 (3)	44 (5)*	70 (3)
ALP	28 (1)	23 (0)	6 (1)	8 (0)
Bilirubin	342 (6)	175 (3)*	31 (4)	95 (4)
History of severe liver chemistry elevation, $n$ (%) <sup>‡</sup>				
ALT	93 (2)	72 (1)*	15 (2)	25 (1)
AST	66 (1)	60 (1)	12 (2)	24 (1)
ALP	8 (0)	7 (0)	2 (0)	6 (0)
Bilirubin	163 (3)	80 (1)*	17 (2)	69 (3)

\* $p$ -value  $< 0.017$  for the comparison with dolutegravir.  
<sup>†</sup>Moderate Elevation: AST, ALT, ALP  $\geq 2.5$  to  $< 5 \times$  ULN or bilirubin  $\geq 1.6$  to  $< 2.6 \times$  ULN.  
<sup>‡</sup>Severe Elevation: AST, ALT, ALP  $\geq 5 \times$  ULN or bilirubin  $\geq 2.6 \times$  ULN.  
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; DRV, darunavir; DTG, dolutegravir; EVG, elvitegravir; RAL, raltegravir.

**Figure 3.** Prevalent liver disorders and liver fibrosis over follow-up ( $n = 16,024$ ).\* $p$ -value  $< 0.017$  for the comparison with dolutegravir.†Moderate Elevation: AST, ALT or ALP  $\geq 2.5$  to  $< 5 \times$  ULN or bilirubin  $\geq 1.6$  to  $< 2.6 \times$  ULN.‡Severe Elevation: AST, ALT or ALP  $\geq 5 \times$  ULN or bilirubin  $\geq 2.6 \times$  ULN.

CI, confidence interval; DILI, drug-induced liver injury; LCE, liver chemistry elevation.

**Table 3.** Prevalence of specific liver chemistry elevations over follow-up ( $n = 16,024$ ).

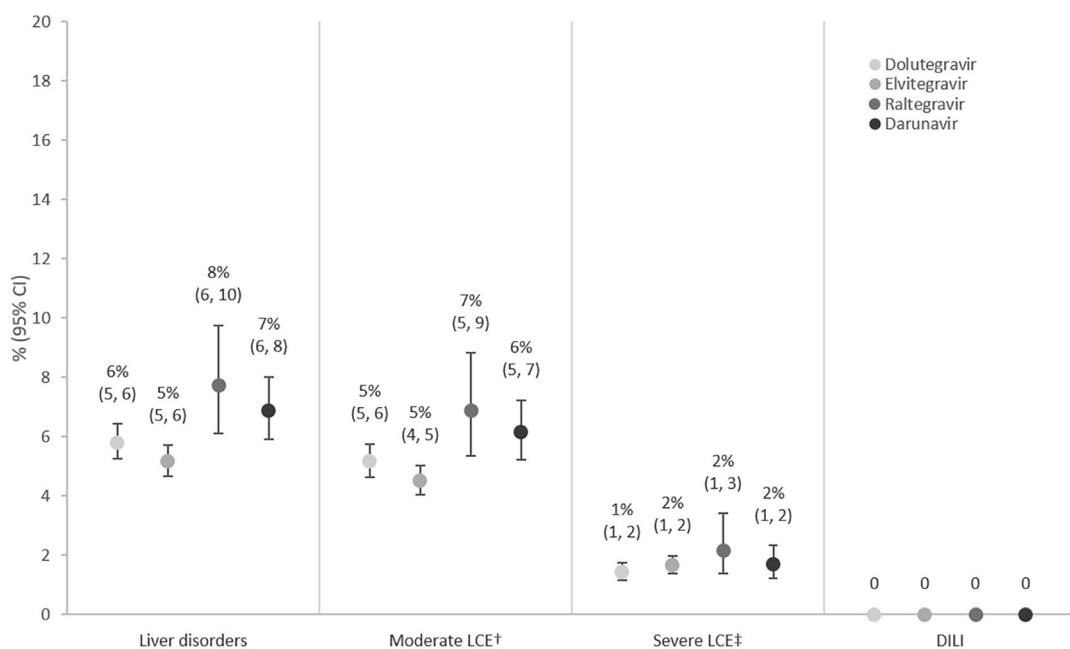
	DTG ( $n = 6102$ )	EVG ( $n = 6899$ )	RAL ( $n = 827$ )	DRV ( $n = 2196$ )
Prevalent moderate liver chemistry elevation, $n$ (%) <sup>†</sup>				
ALT	304 (5)	270 (4)*	59 (7)*	113 (5)
AST	257 (4)	265 (4)	50 (6)*	105 (5)
ALP	41 (1)	29 (0)	10 (1)	30 (1)*
Bilirubin	112 (2)	42 (1)*	39 (5)*	23 (1)*
Prevalent severe liver chemistry elevation, $n$ (%) <sup>‡</sup>				
ALT	97 (2)	114 (2)	21 (3)	44 (2)
AST	81 (1)	96 (1)	18 (2)	45 (2)
ALP	18 (0)	14 (0)	1 (0)	8 (0)
Bilirubin	46 (1)	22 (0)*	20 (2)*	14 (1)

\* $p$ -value  $< 0.017$  for the comparison with dolutegravir.

<sup>†</sup>Moderate Elevation: AST, ALT, ALP  $\geq 2.5$  to  $< 5 \times$  ULN or bilirubin  $\geq 1.6$  to  $< 2.6 \times$  ULN.

<sup>‡</sup>Severe Elevation: AST, ALT, ALP  $\geq 5 \times$  ULN or bilirubin  $\geq 2.6 \times$  ULN.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; DRV, darunavir; DTG, dolutegravir; EVG, elvitegravir; RAL, raltegravir.



**Figure 4.** Incident liver disorders and liver over follow-up ( $n = 16,024$ ).<sup>†</sup>Moderate Elevation: AST, ALT or ALP  $\geq 2.5$  to  $< 5 \times$  ULN or bilirubin  $\geq 1.6$  to  $< 2.6 \times$  ULN.

<sup>‡</sup>Severe Elevation: AST, ALT or ALP  $\geq 5 \times$  ULN or bilirubin  $\geq 2.6 \times$  ULN.

CI, confidence interval; DILI, drug-induced liver injury; LCE, liver chemistry elevation.



**Table 4.** Incidence of specific liver chemistry elevations over follow-up ( $n=16,024$ ).

	DTG ( $n=6102$ )	EVG ( $n=6899$ )	RAL ( $n=827$ )	DRV ( $n=2196$ )
Incident moderate liver chemistry elevation, $n$ (%) <sup>†</sup>				
ALT	182 (3)	173 (3)	27 (3)	81 (4)
AST	142 (2)	177 (3)	21 (3)	60 (3)
ALP	24 (0)	15 (0)	5 (1)	21 (1)*
Bilirubin	50 (1)	25 (0)*	19 (2)*	10 (1)
Incident severe liver chemistry elevation, $n$ (%) <sup>‡</sup>				
ALT	52 (1)	72 (1)	10 (1)	20 (1)
AST	48 (1)	63 (1)	9 (1)	20 (1)
ALP	8 (0)	7 (0)	1 (0)	5 (0)
Bilirubin	14 (0)	13 (0)	6 (1)	4 (0)

\* $p$ -value  $<0.017$  for the comparison with dolutegravir.  
<sup>†</sup>Moderate Elevation: AST, ALT, ALP  $\geq 2.5$  to  $<5 \times$  ULN or bilirubin  $\geq 1.6$  to  $<2.6 \times$  ULN.  
<sup>‡</sup>Severe Elevation: AST, ALT, ALP  $\geq 5 \times$  ULN or bilirubin  $\geq 2.6 \times$  ULN.  
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; DRV, darunavir; DTG, dolutegravir; EVG, elvitegravir; RAL, raltegravir.

severe elevation of ALT.<sup>11</sup> There were no severe elevations of total bilirubin in the STRATEGY-PI trial.<sup>11</sup> Among ART-naïve PLWH in the ONCEMRK trial, the cumulative incidence of moderate LCE with RAL use ranged from 1.5% to 4.5%, depending on the specific liver enzyme; the cumulative incidence of severe LCE ranged from 0.4% to 2.1% and there were zero grade 4 elevations of AST.<sup>10</sup> Among ART-experienced PLWH taking RAL in the BENCHMRK trials, the cumulative incidence of severe LCE ranged from 1% to 4% at 96 weeks, 1% to 5% at 156 weeks, and 2% to 5% at 240 weeks; there was no difference between the RAL and placebo groups.<sup>12</sup> Trials of DRV among ART-naïve PLWH (ARTEMIS trial)<sup>8,25</sup> and ART-experienced PLWH (TITAN study)<sup>13</sup> report combined moderate and severe LCE proportions that ranged from 1% to 9% at 48 weeks and 1% to 13% at 192 weeks. There were only two ( $<1\%$ ) discontinuations due to an adverse event attributed to elevations of ALT in the TITAN study of 298 ART-experienced PLWH.<sup>13</sup>

There are limited observational studies assessing liver outcomes with ART regimens that contain currently common core agents. In the ICONA Cohort of 6575 ART-naïve PLWH, there were 183 moderate or severe elevations of ALT or AST over 20,722 person-years. In multivariable

models, there was a significant decrease in the hazard of those LCE among INSTI users (HR 0.46, 95% CI: 0.25–0.86) compared with NNRTI users; RAL prescription was associated with an even greater risk reduction compared with NNRTIs (HR 0.11, 95% CI: 0.02–0.84). There were 90 severe LCE over 20,983 person-years; there was no difference between core agent groups.<sup>16</sup> The favorable hazard reduction with INSTI use is consistent with our findings in the OPERA cohort. Baldin *et al.* reported that three patients (of 123) discontinued DTG due to hepatic toxicity. There were no discontinuations in the EVG group ( $n=186$ ); baseline ALT and AST levels were similar between the groups.<sup>26</sup> Over 6–12 months of follow-up in the SCOLTA cohort, only 1% of ART-naïve and 1% of ART-experienced PLWH using EVG experienced a severe LCE.<sup>15</sup> Finally, in a 3-year study in Spain of RAL users, only 1% of PLWH developed a grade 3 or 4 hepatotoxicity which were attributed to HCV co-infection. The cumulative incidence of any hepatotoxicity (i.e. grades 1–4) with RAL was only 8% with HIV mono-infection and 25% with HIV-HCV co-infection.<sup>17</sup>

There are several strengths of this study. First, OPERA is a large cohort representing a diverse group of PLWH in care in the US; PLWH were

enrolled from a wide variety of settings, ranging from small, rural clinics and large, urban health centers. At the time of this study, the 84,084 PLWH in the OPERA cohort represented approximately 7% of PLWH in the US.<sup>27</sup> This study utilized EHR that included all clinical interactions, laboratory results, and provider notes, and served as a reflection of real-world clinical practice. The large study population of 16,024 PLWH with liver chemistry tests, both prior to starting a regimen of interest and during follow-up, allowed us to describe both prevalent and incident liver outcomes. Prevalence estimates are important since the burden of liver disorders has implications for care management; estimates of incident outcomes allow us to identify if liver disorders are more common with certain core agents.

This study is not without limitations. Despite important differences between the groups, both in demographics and clinical characteristics that may impact the risk of liver disorders, all comparisons were unadjusted; results are hypothesis generating and should not be used to make inferences on the association between core agents and the occurrence of liver disorders. Some of the differences could have been the result of channeling sicker PLWH from EVG and toward DTG or RAL. While channeling likely played a role in the differences of prevalent and incident liver disorders observed, it is impossible to determine the impact of it on the results as comparisons were unadjusted. PLWH prescribed DTG were more likely to undergo liver chemistry testing than any other group; a higher frequency of testing increases opportunities to detect LCE, and to detect them earlier. Thus, selecting only PLWH with tests performed could have led to selection bias; results must be interpreted accordingly. ART-naïve PLWH may be more susceptible to hepatotoxicity than ART-experienced PLWH. In this study, RAL users were more likely to fall into the former category but results were not stratified by ART experience. Another limitation is that only incidence proportions were calculated (instead of incidence rates). Incidence rates describe how quickly an outcome occurs in a population, person-time is incorporated directly into the denominator, and PLWH who entered the observation period at different times are accounted for. However, in this study, follow-up time was relatively short and similar between groups and loss-to-follow-up was minimal.

In addition to liver outcomes, we examined the incidence of other body system outcomes and disorders in the OPERA cohort as part of a larger study. Several outcomes investigated occurred rarely (incidence proportions <1% for pancreatic disorders, immune reconstitution inflammatory syndrome, hypersensitivity reaction, rhabdomyolysis, severe systemic rash and body fat redistribution or accumulation). Although DTG and RAL were more frequently prescribed to PLWH with a history of disorder, no difference in the incidence of these rare outcomes was detected between core agents.<sup>28</sup> In ART-naïve PLWH, no statistically significant increase in the risk of gastrointestinal (GI) disorders (gastritis, peptic ulcer disease, GI bleeding, GERD, acid reflux, esophagitis, duodenitis, GI ulcerations) over the first 6 months of ART was detected with EVG, RAL, or DRV compared with DTG. ART-experienced PLWH on DRV or RAL were more likely to experience GI disorders than those on DTG in their first 6 months on the regimen.<sup>29</sup> Finally, renal outcomes were also explored; the inhibition of creatinine tubular secretion by some of the ARVs studied resulted in an inflated number of renal impairment events.<sup>30</sup>

In summary, in this large and diverse cohort of PLWH in the US, the incidence of moderate or severe LCE was rare and did not differ between DTG and EVG, RAL, and DRV. Discontinuation following a liver disorder was infrequent, and consistent with prior trials and observational studies, suggesting that the observed severity of liver toxicities associated with these antiretrovirals is low, allowing clinicians to maintain their patients on these core agent-based regimens. These results reinforce the findings from many randomized controlled trials and observational cohort studies in underscoring the liver tolerability of these commonly used core agents. However, more work would be required to fully investigate the degree of severity and persistence of disorders required for discontinuation of treatment.

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### ORCID iDs

Laurence Brunet  <https://orcid.org/0000-0001-8467-4835>

Jennifer Fusco  <https://orcid.org/0000-0003-1556-811X>

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